EXPERIENCE WITH SOFOSBUVIR IN TREATING HCV INFECTED PATIENTS IN TERTIARY CARE HOSPITAL KHYBER PAKHTUNKHWA

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ABSTRACT

Objectives: To determine the efficacy and end therapy response of Sofosbuvir in HCV infected patients attending tertiary care hospital.

Material and Methods: This observational study was conducted at Lady Reading Hospital MTI Peshawar from August 2016 to August 2017. All patients with Chronic Hepatitis C received Sofosbuvir 400mg plus weight based Ribavirin for 24 weeks. Follow up PCR was performed at end of treatment to determine ETR.

Results: A total of 135 patients were enrolled in the study. The mean age was 45.12 years (18.8 ± years).Out of 135 patients, 94(69.20%) were treatment naïve and 41(30.37%) patients were previously treated with interferon and RBV combination. End therapy response (ETR) was 91.89 %(n=102) in genotype 3 while it was 91.66% (n =22) in patients with genotype 1. Among 40 cirrhotic patients, end therapy response was achieved in 97.22% in genotype3, while it was observed in 75.0% of genotype 1 patients.

Conclusion: Sofosbuvir in combination with Ribavirin is effectual and well tolerated in our population.

Key Words: Sofosbuvir, HCV infection, End therapy response (ETR).

INTRODUCTION

Globally, 2.2% of the world population is suffering from hepatitis C virus infection.[1] HCV infection prevalence varies from country to country. In the U.S. and European countries, prevalence is 1.6 to 1.8% and 1.0 to 1.8% respectively[2]. Pakistan is the second most prevalent country for hepatitis C, ranging from 4.5% to 8.0%.[3,4] Within Pakistan, the HCV prevalence rate varies among the four Provinces, highest in Punjab (6, 7%) followed by Sind (5.0%), Baluchistan (1, 5%) and Khyber Pakhtunkhwa (1.1%).[5]

HCV genotype 3a is the predominant genotype in Pakistan followed by 2a.[6,7,8,9,10] In reference to regional distribution in our country, genotype 2a in KPK, while genotype 3a in Punjab and Sind provinces are the principal genotypes.

Worldwide HCV infection is blamed for increasing social, economic and health burden.[11,12] It is daunting to know that 66% population of Pakistan is living in the rural areas.[13] Studies in our country point out that the rate of positivity for HCV is much higher in rural areas than the pre-urban areas.[14] Lack of formal education and awareness, inadequate health care system, improper environmental conditions and poverty are some of the causative elements for HCV infection in our population.[15,16,17,18,19,20]

Treatment of chronic hepatitis has turned around since in the early 1990s from Interferon and Ribavirin to the availability of direct antiviral agents in 2014.[21] The idea of HCV treatment is to achieve a sustained virological response (SVR). SVR is defined as undectable HCV RNA six months after completion of therapy, leading to HCV clearance. IFN- related side effects remain a major problem in clinical routine.[22,23] IFN treatment affects the patient compliance and impedes treatment in cirrhotic patients. Sofosbuvir is an oral Pyrimidine nucleotide analog. It has high potent pan- genotypic antiviral activity and a high genetic barrier to resistance.[24]

Unfortunately, in our country, there is paucity of studies regarding the use of Sofosbuvir. The purpose of this study is to provide an overview of the clinical efficacy and safety of Sofosbuvir in our patients with hepatitis C.

MATERIAL AND METHODS

This open label, single group, observational study was carried out at Lady Reading Hospital, Medical Teaching Institute, Peshawar from August 2016 to August 2017. Patients were recruited through non-probability consecutive sampling technique. Both Pakistani and Afghan national were included. Written Informed consent was obtained from every patient

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before taking part in study. We included all chronic Hepatitis C patients with ages above 18 years and those with compensated Liver cirrhosis. Demographic information including gender, age and address were recorded.

DETECTION AND QUANTIFICATION OF HCV RNA

HCV RNA extraction was done with auto extraction system (SAMAGE, FRANCE) and amplified using Taq man Probe chemistry which is along with primers specially designed to the conserved region of HCV.Due to exonuclease activity and cleavage of probe, florescence of particular wavelength is emitted that is detected by CCD camera in Real TIME PCR machine.

Sensitivity of the assay is less than 35 IU/ml while the specificity is 1-7 genotypes.

Conversion formula for viral load in case of Taq man assay: IU/ml=2 copies/ml

HCV GEONOTYPING

HCV genotyping was done using real time PCR method (Sacace Biotechnologies, Italy) for major Genotype analysis that detects HCV Major Genotypes in HCV positive clinical materials, using real time hybridization-florescence detection.

After baseline evaluation, Sofosbuvir and Ribavirin were prescribed according to international guidelines.[25] All patients were offered Sofosbuvir 400mg once daily while Ribavirin was administered orally in divided doses according to bodyweight (1000mg per day in patients with body weight of <75 kg and 1200mg daily in patients with bodyweight >75 kg)for a period of 24 weeks. Hematological and Biochemical profile was done throughout the duration of therapy. Adverse effects were recorded during the treatment period. Liver cirrhosis was determined by Fibroscan (>14.6 Kpa) and APRI (aspartate aminotransferase to platelet ratio index >2).

The primary efficacy end point of our study was End therapy response (ETR), which is defined as HCV RNA level below the lower limit of quantification,(LLOQ; i.e. <25 IU ml) at completion of 24 weeks of therapy. Our study was approved by the Hospital Ethical Committee (HEC). Data was entered and analyzed using statistical package for social sciences, SPSS version 21.0.

RESULTS

A total of 135 patients were included in our study amongst which 74 (54.8%) were male and 61(45.18%) were female. The mean age of participants was 45.12 years (18.8 ± years). Study participants with Genotype 3 were 111(82, 22%) while 24 (17.77%) patients were found positive for Genotype 1 as shown in Table No. 01.

Among 94(69.20%) treatment naïve patients, genotype 3 were 84(89.36%) and genotype 1 were 10(10.64%). 41 (30.37%) patients were previously treated with interferon and RBV combination, 27 Patients were genotype3 (65.85%) and those with genotype1 were 14 (34.14%). End therapy response (ETR) with 06

Table 1-a. HCV Genotype-3. Treatment Naïve patients.(n=84)

S. No	Liver Status	Total	ETR	
			Achieved	Not Achieved
1	Normal	54	46 (85.18%)	08 (14.81%)
2	Cirrhosis LC-CTP-A	30	29(96.66%)	01(3.33%)
Total		84	75 (89.28%)	09 (10.71%)

Table 1-b. HCV Genotype-3. Treatment Experience patients.(n=27)

S. No.	Liver Status	Total	ETR	
			Achieved	Not Achieved
1	Normal	21	21 (100%)	—
2	Cirrhosis LC-CTP-A	06	06(100%)	—
Total		27	27 (100%)	—

Table 2-a. HCV Genotype-1. Treatment Naive patients.(n=10)

S. No.	Liver Status	Total	ETR	
			Achieved	Not Achieved
1	Normal	10	10 (100%)	—
2	Cirrhosis LC-CTP-A	—	—	—
Total		10	10 (100%)	—

Table 2-b. HCV Genotype-1. Treatment Experience patients. (n=14)

S. No.	Liver Status	Total	ETR	
			Achieved	Not Achieved
1	Normal	10	09 (90.0%)	01(10.0%)
2	Cirrhosis LC-CTP-A	04	03 (75.0%)	01 (25.0)
Total		14	12(85.71%)	02(14.28%)

months treatment was observed in 102 pts with genotype 3 (91.89%), while the response rate was 91.66% (n =22) in pt with genotype 1. as shown in Table No 02. Among 40 cirrhotic pts included in our study, end therapy response was achieved in 97.22% in genotype 3 pts, while it was observed in 75.0% of genotype 1 patients.

DISCUSSION

Hepatitis C is a global challenge. HCV infection is usually slowly progressive over a period of many years. About 80% of patients infected with HCV will become chronically infected and between 05% and 15% of patients with chronic hepatitis C may progress to developing Liver Cirrhosis over a period of 20 years.[26,27,28] There is 1-4% annual risk of developing primary HCC in HCV related liver cirrhosis.[29]

The goal in treating HCV infection is to reduce virus related complications i.e. liver cirrhosis and decompensation, risk of HCC and severe extra-hepatic manifestations. Before the era of Pegylated interferon (PEG-IFN), conventional IFN monotherapy or conventional interferon/Ribavirin (IFN/RBV) combination therapy was the mainstay of HCV treatment in most parts of the world. After 2002 PEG-IFN/RBV became available. All of these treatments left about 50 -60% of chronic hepatitis C patients as either non-responders or relapsers.[28] These therapies required 24-48 weeks of injections with Interferon and Ribavirin. Also this type of treatment was associated with serious side effects. Too many of the patients were either ineligible for IFN or were unwilling to accept treatment due to significant toxicity. A supreme regimen was hence required that would involve all oral drugs, once daily dosage, a short course of therapy with minimal adverse effects. In addition this regimen would be Pan genotypic and have a higher SVR value (95%) regardless of age, race, gender, stage of liver fibrosis and prior non response to IFN/RBV treatment.[30] After 2011 this led to the period of direct –acting antiviral (DAA), which are currently standard of care. Sofosbuvir is easily available in Pakistan at low price.

In the current study HCV RNA level was dramatically declined rapidly after start of therapy and this was maintained till end of treatment. Overall End Therapy response (ETR) was 92.0% among the enrolled patients.

In comparison with standard PEG-IFN /RBV therapy, response rate in our study (92.0%) is much higher. The key clinical trials on PEG-IFN/RBV therapy showed an SVR of 40-45% in patients with genotype 1, 80% in subjects with genotype 2, and only 50% in those with genotype 3a. 28 In a national study conducted at public sector hospital of Karachi, ETR was 86% in those patients who were treated with combination of PEG-IFN /RBV therapy.[31] Basher Ahmad et al, studied the response of standard IFN in HCV patients in four different regions of KPK and ETR was found very low (69.2%).[32]

When comparing to DAAs in combination with RBV, the results of our study are in concurrence with other studies. Like an open –label, single group trial (HEATS), conducted by Zahid Azam, et al the response rate was 98% in HCV patients receiving Sofosbuvir. 33 In another study carried out by Lawitz E, et.al. The response rate was in the range of 90-98 %.(34) Studies have proved RVR and ETR to be a good predictor of SVR.[35]

Regarding treatment experience patients, our results are encouraging when compared to international data. Our study has shown a good response in cirrhotic patients with ETR of 97.22% and 75% in G3 and G1 patients respectively. The most recent VALLENCE trial results in cirrhotic patients after a 24 week drug use in combination with RBV, showed an SVR of 77.0%, which are discouraging.[36] RESIP study from Pakistan also demonstrated SVR of about 86% in treatment experience patients.[37] In an another study conducted by Tayyab Seed Akhtar et.al, 502 G3 infected patients were studied and RVR was about 90%.These results are quite comparable with our study.[38]

No serious side effects were reported during study duration. Only minor complaints were that of headache, fatigue and generalized aches and pain which were easily managed. Blood transfusion was required in only one patient due to Ribavirin related anemia. In a study conducted by Younossiet et.al, similar adverse effects were documented.[39]

CONCLUSION

In conclusion Sofosbuvir in combination with RBV is a major step forward in HCV treatment. This regimen appears to be safer, effective, well tolerated in our population and allows shorter duration of treatment.

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